Air Pollution and Blood Markers of Cardiovascular Risk

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Recent studies have linked air pollution to tens of thousands of premature cardiovascular deaths per year. The mechanisms of such associations remain unclear. In this study we examine the association between blood markers of cardiovascular risk and air pollution in a national sample of the U.S. population. Air pollution concentrations were merged to subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States, and the association with fibrinogen levels and counts of platelets and white blood cells were examined. The subjects in NHANES III are a representative sample of the U.S. population. Regressions controlled for age, race, sex, body mass index, current smoking, and number of cigarettes per day. The complex survey design was dealt with using mixed models with a random sampling site effect. In single-pollutant models, PM_{10} (particulate matter with a mass median aerodynamic diameter less than 10 μm) was associated with all three outcomes ($p < 0.05$): Sulfur dioxide (SO_2) was significantly associated only with white cell counts, nitrogen dioxide (NO_2) with platelet counts and fibrinogen, and ozone with none of the outcomes. In two-pollutant models, PM_{10} remained a significant predictor of white cell counts controlling for SO_2 but not vice versa. PM_{10} was marginally significant in a model for platelet counts with NO_2, and the sign of the NO_2 coefficient was reversed. These results were stable with control for indoor exposures (wood stoves, environmental tobacco smoke, gas stoves, fireplaces), dietary risk factors (saturated fat, alcohol, caffeine intake, n-3 fatty acids), and serum cholesterol. The magnitude of the effects are modest [e.g., 13 μg/dL fibrinogen for an interquartile range (IQR) change in PM_{10}, 95% confidence interval (CI) 4.6–22.1 mg/dL]. However, the odds ratio of being in the top 10% of fibrinogen for the same IQR change was 1.77 (95% CI 1.26–2.49). These effects provide considerable biologic plausibility to the mortality studies. PM_{10}, but not gaseous air pollutants, is associated with blood markers of cardiovascular risk, and this may explain epidemiologic associations with early deaths. *Key words:* air pollution, blood markers, cardiovascular disease, PM_{10}. — *Environ Health Perspect* 109(suppl 3):405–409 (2001).
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The London smog episode of December 1952 resulted in approximately 4,000 excess deaths due to air pollution (*1*). Although the greatest relative increase in mortality was for respiratory causes, the majority of the excess deaths were from cardiovascular disease (*1*). However, most air pollution research in the next several decades focused on the respiratory effects of air pollution.

Beginning in the late 1980s, numerous studies reported associations between air pollution (principally particulate air pollution) and daily deaths in cities in the United States, Europe, Latin America, and Asia (*2–4*). The elevations in risk in these studies were much lower than in London in the 1950s, as were the particle concentrations, but because the exposures associated with the elevated risks occurred daily, the attributable number of early deaths appeared substantial. In addition, the majority of the excess deaths were cardiovascular (*5,6*). More recently, studies have reported that air pollution was associated with hospital admissions for heart disease (*7–9*), including myocardial infarctions. Another set of studies examined the location of deaths associated with air pollution. In 1994, Schwartz (*10*) reported that the greatest relative increase in pollution-associated deaths in Philadelphia, Pennsylvania, USA, was for "dead on arrival" deaths. In a more recent study, Schwartz examined the association between PM_{10} (particulate matter with a mass median aerodynamic diameter less than 10 μm) and daily deaths in 10 U.S. cities and reported air pollution was primarily associated with deaths out of the hospital (*11*). These are mostly sudden deaths, many of which are due to arrhythmia and myocardial infarctions.

In the last 5 years, attention has focused on how air pollution can affect cardiovascular disease. One possibility is that pollution could induce arrhythmia. Animal studies have shown that urban combustion particles can produce reductions in heart rate variability that are risk factors for sudden death (*12*) and death from arrhythmia (*13*). Recently, three papers reported airborne particles were associated with decreases in heart rate variability (*14–16*). Another recent paper reported nitrogen dioxide (NO_2) and $PM_{2.5}$ (particulate matter with aerodynamic diameter less than 2.5 μm) were associated with defibrillator discharges due to ventricular arrhythmias in patients with implanted cardioverter defibrillators (*17*). Increased heart rate has also been associated with airborne particles (*18,19*). These findings suggest compromised autonomic control of the heart may play a role in the cardiovascular toxicity associated with particles.

Daily time–series studies have also indicated that particulate air pollution is associated with deaths (*2*) and hospital admissions for myocardial infarctions (*7*). Seaton et al. (*20*) have proposed that particles may increase pulmonary inflammation, possibly penetrate into the bloodstream, interact with platelets, and trigger systemic increases in coagulability and other risk factors for acute myocardial infarctions. Recently, Peters and co-workers reported an air pollution episode and daily variations in air pollution were associated with increased plasma viscosity (*21*). Gardner and colleagues reported increases in fibrinogen in animals exposed to urban particles (*22*). Human volunteers exposed to concentrated air particles also have increased levels of plasma fibrinogen (*23*). In addition, a recent controlled human exposure study found exposure to diesel particles for 1 hr at 300 $\mu g/m^3$ resulted in increased levels of peripheral neutrophils (*24*). Similar results were reported in rats exposed to concentrated air particles (*25*). In contrast, Seaton et al., in a longitudinal study of 131 subjects, have recently reported that PM_{10} was negatively associated with plasma fibrinogen, and not associated with white blood cells (*26*). Increased levels of fibrinogen and neutrophil counts have been associated with coronary heart disease (*27*). This includes associations with sudden death (*28*) and myocardial infarction (*29*). In addition, elevations of fibrinogen are associated with inflammatory changes such as neutrophil activation (*30*). Studies of such intermediate end points are critical for better understanding how airborne particles might be affecting cardiovascular health. This article examines the association between air pollution and several such intermediate biomarkers of cardiovascular risk in a national sample of subjects chosen to be representative of the U.S. population.

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Data and Methods

Health Data

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted between 1989 and 1994. NHANES III is a stratified random sample of the U.S. population, with oversampling for minorities. Black Americans and Mexican Americans each separately represent 30% of the NHANES III sample. (Some sampled persons are members of both subgroups.) NHANES III also oversampled the elderly. Persons 60 years of age and older represent 20% of the sample but only 16% of the population. The NHANES III sample is equally split by gender. NHANES III was conducted in two phases, each sampling approximately 20,000 subjects in 44 communities. Each phase included individuals representative of the U.S. population. This analysis is restricted to subjects sampled in the first phase.

Subjects were seen in their homes by trained interviewers, and extensive medical history and demographic data were collected. The subjects then visited mobile medical examination centers, where they were examined. Blood specimens for a complete blood count, including platelets, were analyzed at the medical examination center using a Coulter S Plus Jr. The remaining blood was placed in appropriate vials stored under appropriate refrigerated (4–8°C) or frozen (–20°C) conditions until they were shipped to analytical laboratories for testing. Fibrinogen was stored in a 2-mL blue vial. The analytical methods used by each of the participating laboratories are described in Laboratory Procedures Used for NHANES III (*31*). The outcomes of interest in this study were fibrinogen levels, platelet counts, and white cell counts.

Air Pollution Data

Air pollution data was obtained from the Aerometric Information Retrieval System (AIRS) (*http://www.epa.gov/dir/data/contacts.html*) of the U.S. Environmental Protection Agency. AIRS contains information on all of the routine pollution monitoring in the United States. Pollution exposure was assigned to subjects on the basis of geocoding. Each participant in NHANES III was assigned the latitude and longitude of the population centroid of the census block group in which they lived. Block groups are collections of adjoining blocks with populations of 500–1,000 persons. The latitude and longitude of each monitor in the United States was obtained from AIRS. Persons were assigned exposure values equal to the weighted average of all monitors in their county of residence and adjoining counties, with weights proportional to the inverse of the square of the distance between their residence and the monitor. The use of all monitors in the county of residence and adjoining counties allowed geographic variability in exposure within area to be reflected in the exposure measures. This is more important for some pollutants (such as NO_2) more spatially heterogeneous than others (such as ozone). A recent study has shown that within-city variability in NO_2 is associated with pulmonary function (*32*). Exposure values were computed for the day of examination. Exposure the day before the examination was also considered. As subjects were examined for about 6 weeks in each study area, this provided considerable within-area spatial and temporal variability in exposure. The air pollutants collected for this study were PM_{10}, sulfur dioxide (SO_2), NO_2, and ozone (O_3).

Statistical Analysis

The NHANES III was a not a simple random sample. Blacks and Hispanics were oversampled to provide sufficient numbers to allow separate analyses of health parameters in those groups. However, the exact probability of being selected was computed for each participant, and from that sampling, weights were computed. The use of weighted statistical analyses provides estimates representative of the U.S. noninstitutionalized population.

For sampling convenience the sampling strategy first selected 44 counties in the United States, then subjects within those counties. Because of regional differences in ethnicity, diet, and other factors, all of which may not be perfectly controlled for in a given analysis, the residuals of two persons chosen from the same county are likely to be more alike than the residuals from two persons randomly chosen from different locations. That is, there tends to be correlation with the sampling units. Mixed models, which allow for regression analyses with a covariance structure assuming a common correlation within these sampling units, provide proper standard error estimates for the regression parameters under these circumstances. This analysis used PROC MIXED in SAS (SAS Institute, Cary, NC, USA), with a random effect for each location in the survey, assuming a compound symmetry covariance structure. The final examination weights were also used. For estimates of the proportion of the population with high fibrinogen levels (or high white cell or platelet counts), I used PROC GENMOD to fit logistic regressions, with generalized estimating equations and an exchangeable covariance structure.

All regression analyses controlled for age, ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanics, and others), body mass index, a dummy variable for current smoker, cigarettes per day, and sex. PM_{10}, SO_2, NO_2, and O_3 were examined as potential predictors of the three outcome variables in single-pollutant models. If more than one pollutant was a significant predictor of an outcome in those models, multipollutant models were examined.

Sensitivity Analysis

To examine the potential of other variables to confound the association, I took two approaches. First, I examined the effect estimates for air pollution in models with and without all of the potential confounders added to the baseline model one at a time. Then, for each outcome, I identified all the covariates that were marginally significant ($p < 0.10$) when added singly to the baseline model. The pollution models were then re-estimated with all of these covariates included simultaneously. The potential confounders fell into four categories: social risk factors, dietary risk factors, other indoor exposures, and other cardiovascular risk factors.

Social risk factors. One issue raised about previous reports of associations between particulate air pollution and daily deaths in two recent prospective cohort studies (*33,34*) was that they did not control for socioeconomic status or diet. If air pollution was correlated with these factors, they might have the potential to confound air pollution associations. I used the number of years of education of the subject, the poverty income ratio (the ratio of household income to the city specific poverty level), and their household size as indicators of social status, and examined their potential to confound the association.

Dietary risk factors. If persons in locations of high air pollution are more likely to eat an unhealthful diet, this might also confound the association. To examine whether diets that are potential risk factors for ischemic heart disease were confounders, I used dietary intake of saturated fat, alcohol consumption, and caffeine intake (defined as the sum of the average daily cups of caffeinated coffee plus half the number of daily cups of caffeinated tea). To examine dietary factors that might be protective for ischemic heart disease, I used dietary intake of fish and shellfish (as a proxy for n-3 fatty acid intake) and serum levels of vitamin C.

Other exposures. Recent studies have shown that outdoor concentrations of airborne particles are reasonable surrogates for personal exposure to particles of outdoor origin (*34,35*), but that there are substantial exposure to particles from indoor sources. As these particles have different chemical compositions as well as sources, they are best thought of as other exposures. If they are correlated with outdoor particle concentrations

and with outcome, they may confound the association with the outdoor pollutant. We had variables that provided at least some assessment of many of the major indoor sources. For environmental tobacco smoke, we had an indicator variable for passive smoking in the home, as well as a serum cotinine measurement. We also had indicator variables for use of a wood stove, use of a gas stove, and use of a fireplace.

Other ischemic risk factors. The other major risk factors for ischemia we examined were systolic blood pressure, total serum cholesterol, and serum high-density lipoprotein cholesterol.

Results

Air pollution data were available only for subjects who resided in urban areas, and all pollutants were not monitored in each area of the United States during the study period. In addition, PM_{10} was not measured every day in most locations, so the number of individuals with PM_{10} measurements was substantially less than for the other pollutants. Table 1 shows, for each of the pollutants, the mean, standard deviation (SD), interquartile range (IQR), number of sampling locations for which measurements were available, and number of persons with measurements. Variation in exposure was due to three factors. First, persons were seen in each sampling location over about a 6-week period, providing temporal variation in exposure. Second, exposure levels differed across the 44 locations. Finally, the use of geocoding allowed different persons examined on the same day in the same city to be assigned different exposure values based on the estimated concentrations where they lived.

Table 1. Environmental variables in NHANES III.

Pollutant	Mean	IQR	SD	No. of locations	No. of obs
PM_{10} (μg/m^3)	35.2	26	20.5	30	1,373
NO_2 (ppb)	27.9	19	18.5	24	3,704
O_3 (ppb)	24.1	17	12.4	35	5,245
SO_2 (ppb)	17.2	17	14	25	3,860

obs, observed.

Table 2 shows the descriptive statistics for other data used in the analysis. Table 3 shows results of the initial analyses for air pollution. After controlling for age, race, sex, body mass index, and smoking, PM_{10} was associated with all three outcomes. Platelet counts and plasma fibrinogen were associated with NO_2, and white cell counts with SO_2 in single-pollutant models. In two-pollutant models, only PM_{10} continued to show a positive association with the three outcomes.

Table 4 shows the results of the sensitivity analyses for PM_{10} that investigated a wide variety of potential confounders. The PM_{10} results were quite robust to inclusion of these terms. In general, the effects of the potential confounders were not even consistent, raising the PM_{10} effect estimates for some outcomes, but lowering them for others. The final model, using all covariates with even marginal associations with the outcomes simultaneously, further confirms the robustness of the results.

To put these results in context, Table 5 shows the relative odds of a high level of fibrinogen (426 mg/dL, the 90th percentile of the distribution for fibrinogen in this population), high platelet count (364, also the 90th percentile), and high white cell count (10, again the 90th percentile) associated with an IQR increase in PM_{10}.

Table 2. Distribution of variables used in the analysis: NHANES III.

Variable	Mean	IQR	SD
Outcome measures			
Serum fibrinogen (mg/dL)	318	96	89
Platelet count	274	88	73
White cell count	7.2	2.7	2.3
Baseline covariates			
Age	49	34	20
Female	53%	NA	NA
White	42%	NA	NA
Black	28%	NA	NA
Hispanic	26%	NA	NA
Body mass index (kg/m^2)	27	7	5.8
Current smoker	27%	NA	NA
Cigarettes/day (smokers only)	15		12
Potential confounders			
Social factors			
Poverty/income ratio	2.41	2.26	1.77
Education (total years)	10.9	4.0	3.8
Household size	3.5	2.0	2.3
Other exposures			
Wood stove use	7.9%	NA	NA
Fireplace use	14%	NA	NA
Gas stove use	55%	NA	NA
Environmental tobacco smoke at home	39%	NA	NA
Serum cotinine (ng/mL)	76	94	145
Dietary and other risk factors			
Caffeine (drinks/month)	33	38	50
Dietary alcohol (g/day)	8.9	0	28
Dietary saturated fat (g/day)	25	18	16
Serum vitamin C	0.76	0.63	0.46
Dietary fish and shellfish (portions/week)	5.7	6	7
Serum cholesterol (total, mg/dL)	207	57	45
Serum HDL (mg/dL)	51	19	16
Systolic blood pressure (mmHg)	126	25	20

NA, not applicable.

Table 3. Regression coefficients (standard errors) for the association of air pollutants with cardiovascular risk factors in blood: NHANES III.

Outcome	PM_{10}	O_3	SO_2	NO_2
Single-pollutant models				
Fibrinogen	0.514 (.172)	0.159 (0.152)	0.132 (0.158)	0.408 (0.147)[a]
Platelets	0.316 (.113)[a]	0.072 (0.091)	0.017 (0.094)	0.380 (0.094)
White cells	0.0062 (.0026)	–0.0037 (0.0027)	0.0066 (0.0027)	–0.0022 (0.0027)
Two-pollutant models				
Fibrinogen	0.917 (0.213)			–0.867 (0.369)
Platelets	0.186 (0.117)			–0.439 (0.231)
White cells	0.0083 (0.0026)		–0.0021 (0.0042)	

[a]Exposure from previous day; same day exposure for all other models.

Discussion

I found significant, consistent associations between PM_{10} and the three cardiovascular risk factors examined. In contrast, no consistent associations were found for the gaseous pollutants. Unfortunately, carbon monoxide data were not matched to subjects in this study, so nothing can be said about that pollutant. Moreover, the odds ratios in Table 5 for the risk difference between the highest and lowest quartile of exposures in the United States were substantial.

These findings contrast with those of Seaton and co-workers (*26*), who reported a negative association between PM_{10} concentrations and plasma fibrinogen in a panel study of 131 subjects in Edinburgh, Scotland. However, they are consistent with the results of a controlled human exposure

Table 4. Sensitivity analysis of effect of PM_{10} on cardiovascular risk factors in blood: NHANES III.

Covariate	Fibrinogen	Platelets	White cells
None (baseline)	0.514 (0.172)	0.316 (0.113)	0.0062 (0.0036)
Social factors			
Poverty ratio	0.387 (0.185)	0.270 (0.119)	0.0059 (0.0029)
Education (years)	0.481 (0.173)	0.309 (0.114)	0.0056 (0.0026)
Household size	0.516 (0.173)	0.315 (0.113)	0.0061 (0.0026)
Other exposures			
Wood stove	0.518 (0.173)	0.315 (0.115)	0.0058 (0.0026)
Fireplace	0.516 (0.173)	0.317 (0.114)	0.0062 (0.0026)
Gas stove	0.532 (0.174)	0.289 (0.118)	0.0056 (0.0027)
Environmental tobacco smoke at home	0.514 (0.172)	0.312 (0.114)	0.0062 (0.0026)
Serum cotinine	0.495 (0.174)	0.365 (0.116)	0.0064 (0.0023)
Dietary factors			
Serum vitamin C	0.500 (0.176)	0.342 (0.115)	0.0059 (0.0027)
Fish and shellfish	0.518 (0.172)	0.320 (0.115)	0.0062 (0.0026)
Saturated fat	0.508 (0.175)	0.357 (0.117)	0.0061 (0.0025)
Caffeine	0.523 (0.173)	0.306 (0.113)	0.0062 (0.0026)
Alcohol	0.505 (0.176)	0.411 (0.115)	0.0082 0(.0025)
Cardiovascular risk factors			
Systolic blood pressure	0.540 (0.173)	0.310 (0.113)	0.0066 (0.0025)
Serum cholesterol (total)	0.502 (0.172)	0.353 (0.115)	0.0062 (0.0025)
Serum high density lipoprotein	0.488 (0.172)	0.356 (0.114)	0.0063 (0.0025)
Final model[a]	0.476 (0.173)	0.383 (0.115)	0.0074 (0.0025)

[a]Baseline model plus all covariates univariately associated with the outcome with $p < 0.10$.

Table 5. Relative odds for being above the 90th percentile for fibrinogen, platelet count, and white cell count associated with an IQR increase in PM_{10}.

Outcome	Odds ratio	95% CI
High fibrinogen	1.77	1.26, 2.49
High platelet count	1.27	0.97, 1.67
High white cell count	1.64	1.17, 2.30

study that reported increases in plasma fibrinogen (*35*), as well as with the animal study (*22*). While further results will be necessary to sort out the conflicting reports in epidemiologic studies, the weight of the evidence suggests that airborne particles are associated with increases in fibrinogen.

Likewise, Seaton and co-workers (*26*) did not find increases in white cell counts, whereas Salvi and colleagues (*24*) reported increases in peripheral neutrophils following controlled human exposures to particles. Our results confirm the report of Salvi and coworkers and extend it to the general population and substantially lower exposure levels.

One important result of this study is the examination of confounding by indoor sources of pollution. Some have criticized the use of outdoor air pollutants because they do not incorporate those indoor exposures. However, there are important differences between environmental tobacco smoke, for example, and particles of outdoor, ambient origin. No evidence has ever been presented to demonstrate that these pollutants are the same or have the same health consequences. Hence, it is more appropriate to treat them as two pollutants and ask whether the indoor exposures are confounders for the outdoor exposures. This study, on a nationally representative sample of the U.S. population, suggests this is not the case. Neither measures of indoor particle sources (wood-burning stoves and fireplaces, environmental tobacco smoke), nor measures of indoor NO_x exposures (gas stoves) appeared to confound the associations reported here. Given the representativeness of the sample, this suggests other large cross-sectional studies of the association between particle exposure and health effects, such as the American Cancer Societies CPS II study (*29*), are also unlikely to be confounded. These results are also consistent with the recent exposure work of Sarnat and co-workers (*36*). Using personal exposure monitors, they were able to estimate exposure to particles of ambient origin and of indoor origin in several cohorts. No correlation between the two measures was found.

Socioeconomic confounding has been posited as a possible explanation for some previous cross-sectional findings, such as the Six City Study reports (*33*) of associations between air pollution and life expectancy. The results from this study do not support that hypothesis. The NHANES III had detailed information on income, as well as social factors such as years of education, and these variables did not produce a major perturbation in the air pollution associations. Similarly, dietary risk factors do not seem to be important confounders of the association between air pollution and risk factors for ischemic events.

One important caveat for this study involves the implications of the outcome measures. Fibrinogen and white blood counts have been associated with increased risk of cardiovascular mortality in prospective cohort studies. In those studies a one-time measurement of these risk factors was taken as a measure (with error) of the longer-term levels in each subject and associated with longer-term risk. This study reports associations between short-term exposure to particles and fibrinogen and other risk factors. The extent to which short-term fluctuations in fibrinogen levels result in short term fluctuations in cardiovascular risk is unclear.

What this study does provide, however, is evidence that particulate air pollution can influence important circulatory parameters that are risk factors for adverse events in some circumstances. Such changes could not occur if particles, constituents of particles, or chemical messengers resulting from particle exposures were not passed from the lung to the circulation. Such changes imply that important cardiovascular factors can be modified by airborne particles at commonly occurring concentrations. This provides considerable biologic plausibility for the associations reported in previous epidemiologic studies.

References and Notes

1. Mortality and Morbidity during the London Fog of December 1952. Report no 95 on Public Health and Medical Subjects, Her Majesty's Public Health Service. London:Her Majesty's Stationery Office, 1954.
2. Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak D, Sunyer J, Bacharova L, et al. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br Med J 314:1658–1663 (1997).
3. Borja-Aburto VH, Loomis DP, Shrinkant IB, Shy CM, Mascon-Paceco RA. Ozone, suspended particles, and daily mortality in Mexico City. Am J Epidemiol 145(3):258–268 (1997).
4. Pope CA III, Dockery DW, Schwartz J. Review of epidemiologic evidence of health effects of particulate air pollution. Inhal Toxicol 7:1–18 (1995).
5. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 145:600–604 (1992).
6. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? J Air Waste Manag Assoc 46:2–14 (1996).
7. Schwartz J, Morris R. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:22–35 (1995).
8. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10:17–22 (1999).
9. Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JF. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22 (1995).
10. Schwartz J. What are people dying of on high air pollution days? Environ Res 64:26–35 (1994).
11. Schwartz J. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ Health Perspect 108:563–568 (2000).
12. Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull B, Reinisch U, Lovett EG, Lawrence J, Murthy GG, Wolfson JM, et al. Mechanisms of morbidity and mortality from exposure to ambient air particles. Res Rep Health Eff Inst 91:5–88; discussion 89–103 (2000).
13. Watkinson WP, Campen MJ, Costa DL. Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol Sci 41(2):209–216 (1998).
14. Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Dockery DW. Heart rate

variability associated with particulate air pollution. Am Heart J 138:890–899 (1999).
15. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525 (1999).
16. Gold DR, Litonjua A, Schwartz J, Verrier M, Milstein R, Larson A, Lovett E, Verrier R. Ambient pollution and heart rate variability. Circulation 101:1267–1273 (2000).
17. Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh A, Allen G, Monahan K, et al. Air pollution and incidences of cardiac arrhythmia. Epidemiology 11:11–17 (2000).
18. Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution: a daily time series panel study. Am J Respir Crit Care Med 159:365–372 (1999).
19. Peters A, Perz S, Doring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. Am J Epidemiol 150(10):1094–1098 (1999).
20. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. Lancet 345:176–178 (1995).
21. Peters A, Doring A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349:1582–1587 (1997).
22. Gardner SY, Lehmann JR, Costa DL. Oil fly ash-induced elevation of plasma fibrinogen levels in rats. Toxicol Sci 56(1):175–180 (2000).
23. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in health human volunteers. Am J Respir Crit Care Med 162:981–988 (2000).
24. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 159(3):702–709 (1999).
25. Gordon T, Nadziejko C, Schlesinger R, Chen LC. Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. Toxicol Lett 96–97:285–288 (1998).
26. Seaton A, Soutar A, Crawford V, Elton R, McNerlan S, Cherrie J, Watt M, Agius R, Stout R. Particulate air pollution and the blood. Thorax 54:1027–1032 (1999).
27. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 279:1477–1482 (1998).
28. Benchimol D, Dubroca B, Bernard V, Lavie J, Paviot B, Benchimol H, Couffinhal T, Pillois X, Dartigues J, Bonnet J. Short and long term risk factors for sudden deaths in patients with stable angina. Int J Cardiol 76(2–3):147–156 (2000).
29. Lind P, Hedblad B, Stavenow L, Janzon L, Eriksson KF, Lindgarde F. Influence of plasma fibrinogen levels on the incidence of myocardial infarction and death is modified by other inflammation-sensitive proteins: a long–term cohort study. Arterioscler Thromb Vasc Biol 21:452–458 (2001).
30. Rubel C, Fernandez GC, Dran G, Bompadre MB, Isturiz MA, Palermo MS. Fibrinogen promotes neutrophil activation and delays apoptosis. J Immunol 66:2002–2010 (2001).
31. Laboratory Procedures used for NHANES III. Washington, DC:U.S. Public Health Service, 1996.
32. Schindler C, Ackermann-Liebrich U, Leuenberger P, Monn C, Rapp R, Bolognini G, Bongard JP, Brandli O, Domenighetti G, Karrer W, et al. Associations between lung function and estimated average exposure to NO_2 in eight areas of Switzerland. The SAPALDIA Team. Swiss Study of Air Pollution and Lung Diseases in Adults. Epidemiology 9(4):405–411 (1998).
33. Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329(24):1753–1759 (1993).
34. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674 (1995).
35. Devlin RB, Cascia W, Kehrl H, Ghio A. Changes in heart rate variability in young and elderly humans exposed to concentrated ambient air particles. Am J Respir Crit Care Med 161(3):A239 (2000).
36. Sarnat JA, Koutrakis P, Suh H. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 50:1184–1198 (2000).